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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,642	12/27/2005	Alessandro Sette	EPI - 103X	5117

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EXAMINER	
TONGUE, LAKIA J	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,642	SETTE ET AL.	
	Examiner	Art Unit	
	LAKIA J. TONGUE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-69* is/are pending in the application.

4a) Of the above claim(s) *65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-64 and 66-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/5/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 45-69 are pending. Claims 66-69 have been added. Claim 65 has been previously withdrawn. Claims 45-64 have been amended. Claims 45-64 and 66-69 are currently under examination.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on June 5, 2009 is in compliance with the provisions of 37 CFR 1.97 and has been considered. An initialed copy is attached hereto.

Objections Withdrawn

2. In view of Applicant's amendment, the objection to claims 45, 47, 49, 50, 52, 54, 55, 57, 59, 60, 62 and 64 because on first sight the acronym "HLA" should be followed by "Human Leukocyte Antigen" is withdrawn.

Rejections Withdrawn

3. In view of Applicant's amendment, the rejection of claims 45, 55, 58-60, 63 and 64 under 35 U.S.C. 102(b) as being anticipated by Invitrogen catalog (1997, cDNA synthesis and Libraries) is withdrawn.

4. In view of Applicant's amendment, the rejection of claims 55-64 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the

claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The rejection of claims 45-64 and 66-69 under 35 U.S.C. 112, first paragraph previously rejected over claims 45-64, as failing to comply with the written description requirement because the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for the reasons set forth in the previous office action.

Applicants argue that:

1) Those of ordinary skill in the art would have been able to screen peptide compositions for the recited HLA binding activity in animals and humans in view of the teachings of the specification and the state of the art at the time the application was filed.

2) The instant specification provides instructions for how a skilled artisan could go about identifying and screening HLA binding fragments.

3) Structural determinants are not required to identify and circumscribe the polynucleotides encoding the recited fragments, or polynucleotides fully complementary to polynucleotides encoding such fragments.

Applicant's arguments have been considered but are deemed non-persuasive.

The rejected claims are drawn to an isolated or purified polynucleotide: a) encoding a polypeptide comprising SEQ ID NO: 1; b) encoding a Human Leukocyte Antigen (HLA) binding fragment of SEQ ID NO: 1, said fragment comprising at least five consecutive amino acids of SEQ ID NO: 1; or c) that is complementary along the full length of said polynucleotide of a) or b). Subsequent claims are drawn to a vector comprising a promoter operably linked to a polynucleotide and a transformed host cell comprising a polynucleotide: a) encoding a polypeptide comprising SEQ ID NO: 1; b) encoding a HLA binding fragment of SEQ ID NO: 1; or c) that is complementary to the polynucleotide of a) or b).

With regard to Points 1 and 2, the skilled artisan cannot envision the detailed chemical structure of the claimed polynucleotides or the binding fragment which will encodes a Human Leukocyte Antigen (HLA) of SEQ ID NO: 1, wherein said fragment comprising at least five consecutive amino acids of SEQ ID NO: 1. The core structure has not been identified, consequently, which fragment will bind appropriately is unknown. The claims encompass a genus of polynucleotides which are to be encoded by said polypeptides and binding fragments, which are not adequately described. As taught in basic immunology texts, an epitope or antigenic determinant interacts with its corresponding antibody based on the three-dimensional structure of both molecules and

the fit between them (Cruse et al., Illustrated Dict. of Immunology, 2nd ed., CRC Press, 2003, page 46). These epitopes can be conformational (or discontinuous) epitopes which are formed from separate regions in the primary sequence that are brought together by proper protein folding. Antibodies which bind to conformational epitopes will only bind to proteins folded into their proper native state (Cruse *et al.*, page 166). There are also linear epitopes, which are regions of six amino acids in the primary sequence of a protein. These are generally not found on the surface of a folded protein and are only available to antibodies upon denaturation of a protein (Cruse *et al.*, page 382). Conformational epitopes are only found in a properly folded protein and can contain discontinuous portions of the protein, there is no way that one could determine whether a given polypeptide would bind to the antibody unless this was empirically tested. Any change (including deletions and substitutions), anywhere along the polypeptide is likely to alter the three-dimensional structure and folding of the protein, thus altering the antibody-antigen interaction. This is further supported by other authors such as McGuinness et al. (Mol. Microbiol., 7:505-514, 1993) and Moudallal et al. (EMBO Journal, 1:1005-1010, 1982), who have shown that amino acid deletions, even outside an epitope will alter protein conformation and change antibody-antigen binding.

Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and

which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function.

With regard to Point 3, while the specification fully represents SEQ ID NO: 1 a skilled artisan would not appreciate that Applicants were in possession of an isolated purified polynucleotide encoding a Human Leukocyte Antigen (HLA) binding fragment of SEQ ID NO: 1, said fragment comprising at least five consecutive amino acids of SEQ ID NO: 1; or c) that is complementary along the full length of said polynucleotide of a) or b). Moreover, written description *requires possession of that which has been claimed, not just the means of isolation*. Based on the instant specification, the skilled artisan cannot envision the detailed chemical structure of the claimed polynucleotide. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus.

As previously presented, to fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus of polynucleotides or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession of the claimed invention.

A representative number of species means that the species which are adequately described are representative of the entire genus. The written description

requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The specification lacks a full description of which polynucleotide, vector and transformed host cell comprising a polynucleotide will encode any HLA binding fragment of SEQ ID NO: 1or its complementary polynucleotide. The specification is silent with regard to which specific immunoepitopes are capable of encoding any HLA binding fragment of SEQ ID NO: 1 or its complementary polynucleotide. The specification discloses SEQ ID NO: 1, but does not provide structure correlated with function.

As evidenced by Greenspan et al. (Nature Biotechnology 17: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows the epitope to which any given antibody binds can only be identified

empirically. Even using a competition assay, the skilled artisan cannot determine whether an antibody binds the same epitope as another antibody because an antibody that competes with another does not necessarily bind the same epitope as the other; rather, one antibody may bind a spatially overlapping epitope to sterically hinder binding of the other.

The skilled artisan cannot envision the detailed chemical structure of the claimed isolated or purified polynucleotide, which encodes a HLA binding fragment of SEQ ID NO: 1 or its complementary polynucleotide. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

The University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that: ...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the

inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2datl966.

Further, Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 66-69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has added claims 66-69 to recite "....wherein said HLA binding fragment has a length from the group consisting of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 and 35 amino acids". This phrase does not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent. To overcome this rejection Applicant must specifically point out the support for this limitation or cancel the new matter from the claims.

Conclusion

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKIA J. TONGUE whose telephone number is (571)272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert B Mondesi/
Supervisory Patent Examiner,
Art Unit 1645

LJT
6/10/09